

Pro-Inflammatory cytokine IL-1 in Central Nervous and Reproductive systems in Multiple Sclerosis female patients. Communication between Nervous, Endocrine and Immune system

Ana Frances

Institute of Investigo, Spain

GENERAL ASPECTS

Multiple Sclerosis (MS) is a complex disorder of the central nervous system (CNS) characterized by inflammation, demyelination, and axonal degeneration. The concept that sex hormones may play a role in MS pathogenesis and disease activity is based on two well-established clinical observations: a higher prevalence of MS in females compared to males and a decrease in disease activity during pregnancy, in particular, in the third trimester. In the literature, studies demonstrate significant differences between female and male brain, at molecular and cellular levels as well as its structure. All these features have been called Dimorphism (two forms in the same specie). The Sry gene (sex determining region of the Y chromosome) is the responsible of sexual differentiation of the brain and is originated from work on the hypothalamus once the fetal testes have been formed, releasing 17 β -estradiol.

IL-1 gene family has been implicated in the pathophysiology of multiple sclerosis (MS), where IL-1 α and IL-1 β has been found in MS lesions, as well as increased serum interleukin-1 receptor antagonist (IL-1ra).

Estrogens act as protective hormones in neurons, in several models of neurodegeneration, including disorders caused by excitotoxicity and oxidative stress. It is relevant to notice the communication between nervous, endocrine and immune systems.

DIMORPHISM IN MS

In the literature, many studies demonstrate significant differences between female and male brain specially at hormonal level, when androgens are converted to estrogens by brain P-450 aromatase organizing male-type neural circuitry irrespective of the genetic sex, however, subsequent genetic studies on human subjects with mutations in genes involved in sexual differentiation do not seem to be compatible with the classical steroid hypothesis. Mutations in estrogen receptor or aromatase genes did not correlate with phenotypic gender identity and sexual orientation. This bring us to the conclusion that neurons are capable of achieve sex-specific properties independently of their hormonal environment.

At genetic level, it has been proved that gene products are highly conserved DNA-binding proteins and thus putative transcription factors, ZFY (zinc finger Y-chromosomal protein) and SRY a member of the high- mobility group (HMG)-box protein family. Those genes are involved in sex determination of the gonad, which are transcribed in hypothalamus, and frontal and temporal cortex of the adult male human brain. These genes are crucial for male-specific transcriptional regulators in cells for hormone-independent realization and maintenance of genetic sex. Sertoli cells are the location of the sex region of the Y chromosome (SRY) expression. Therefore, the Sertoli cell arranges the development of primordial germ cells into testis.

SRY is located in the Y chromosome band Yp11.3 and encodes a transcription factor that is a member of the high mobility group (HMG)-box family of DNA binding proteins.

The function of ZFY is still undetermined but remains an interesting gene with a potential role, in its own right, in male sexual development.

Using MRI, women have more inflammatory but less destructive lesions than men. In male MS lesions, there is an estrogen synthesis and ER-mediated signaling; whereas in female MS lesions the main role is represented by progesterone synthesis and signaling. These data indicate that, in response to MS pathology, male MS patients predominantly activate estrogen pathways, whereas females predominantly activate progesterone pathways.

It can be concluded that in male patients, the major changes were the local induction of estrogen synthesis and signaling in MS plaques and the expression of aromatase, (a key enzyme in the synthesis of estrogens), is increased in male MS lesions compared with that in females.

BIOCHEMISTRY

GnRH (gonadotropin-releasing hormone) plays an important role mainly in the development of male hypothalamus circuit via estrogen receptors (ERs), which can explain the GnRH/LH response.

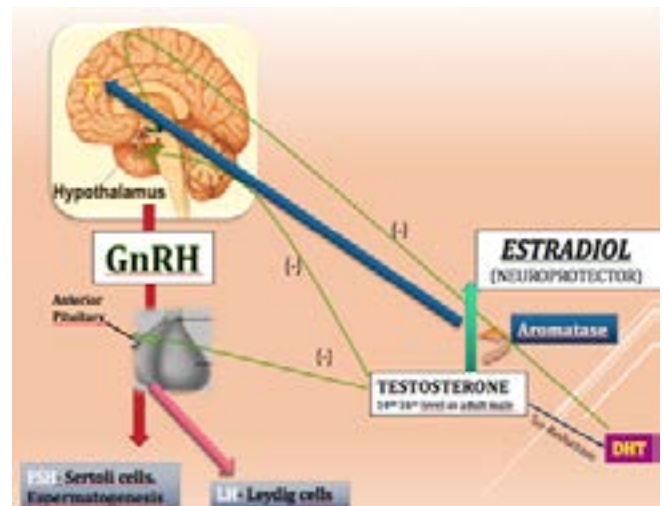


Fig 1: Pattern of the GnRH role in the development of male hypothalamus circuit via estrogen receptors (ERs), which can explain the GnRH/LH response

Testosterone freely enters onto the brain and, in certain regions, its ability to sculpt the male brain, depends, mainly on its conversion to estradiol by local aromatase enzyme and exerts a negative feed-back in Pituitary gland and Hypothalamus when T level raises up. (<http://www.daviddarling.info/encyclopedia/H/hypothalamus.html>).

The levels of gonadotrophin-releasing hormone (GnRH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH), increase on the pubertad onset, and they act as immuno-stimulator in the background of MS and explains why MS risk raises up at post-puberty. Returning at the onset stage, the amplitude of GnRH pulses from hypothalamic neurons, increases and generates a higher pulsatile secretion of LH and FSH from the anterior pituitary.

Recently, researcher studies on a possible neuroprotective effect of testosterone are very frequent in the literature. Testosterone (T) in its free form can cross the blood-brain-barrier and thus directly influence neuronal cells. T ability to sculpt the male brain, depends, mainly on its conversion to estradiol by local aromatase enzyme and exerts a negative feed-back, when its level rises up. (Gillies, G.E, 2002). Testosterone has been shown to protect spinal cord neurons in culture from glutamate toxicity. Testosterone as well as dehydrotestosterone (DHT), which cannot be converted to estrogen, can induce neuronal differentiation and increases in neurite outgrowth in cultured neuronal cells. Women with

MS have lower estradiol levels during the luteal phase and lower (but significant), plasma testosterone concentrations than normal subjects and more brain lesions detected by MRI while men with RRMS or SPMS and healthy men had generally similar sex hormone levels a subset of male MS patients had lower testosterone levels but higher estradiol levels in men with MS were associated with a greater degree of brain tissue damage revealed by the extent of T2 hyperintense and T1 hypointense lesions.

Because oestrogen is a neuroprotective and neuroactive hormone, can be considered as a potential clinical hormone for CNS diseases. After testosterone aromatization oestrogenic compounds can protect brain cells against injury from citotoxicity, oxidative stress, inflammation, ischaemia and apoptosis.

In vitro and *in vivo* preclinical research confirms oestradiol interactions with central neurotransmitter systems and it is implicated in the pathogenesis of schizophrenia.

Estrogen receptor (ER)-dependent influences on processes such: neurogenesis, apoptosis, cells distribution within specific regions or nuclei, neuronal and synaptic density and size, maturation and migration, neurite growth and synaptogenesis, angiogenesis, plasticity and connectivity, axonal sprouting and remyelination, expression of neurotrophic factors.